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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,974	02/08/2002	Lhing-Yew Li		3799

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,974	LI ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-42* is/are pending in the application.

4a) Of the above claim(s) *24 and 40-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15-23 and 25-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 July 2002 and 09 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Status of the Application

[1] The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

[2] Claims 1-13 and 15-42 are pending in the application.

[3] Applicants' amendment to the claims, filed on 6/14/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims. It is noted that the addition of "and wherein said ORF2 polypeptide increases lysine synthesis" in claim 3 is not underlined in accordance with the revised amendment practice of 37 CFR 1.121. Also, claims 5-6 are identified as "currently amended," however, neither of the claims appears to have been amended, and even if the claims are amended, there are no markings to show changes made. Applicants are advised to comply with the revised amendment format according to 37 CFR 1.121.

[4] Applicants' amendment to the specification, filed on 6/14/2005, is acknowledged.

[5] Receipt of a supplemental application data sheet, filed on 6/14/2005, is acknowledged.

[6] Receipt of a petition for priority, filed on 6/14/2005, is acknowledged. The petition has been granted for those reasons set forth in the Office communication mailed on 8/3/2005.

[7] Applicants' arguments filed on 6/14/2005 have been fully considered and are deemed to be persuasive to overcome some of the objections and/or rejections

previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[8] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[9] Claims 24 and 40-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/21/2003.

Claim to Domestic Priority

[10] Applicants' petition for acceptance of a late claim for priority has been granted. In view of the granting of the petition, applicants' claim for domestic priority under 35 U.S.C. § 120 to US non-provisional application 09/722,441, filed 11/28/2000, now US Patent 6,927,046, which claims priority under 35 U.S.C. § 119(e) to US provisional applications 60/184,130, filed 2/22/2000, and 60/173,707, filed 12/30/1999, is acknowledged. The examiner further acknowledges applicants' claim for domestic priority under 35 U.S.C. § 119(e) to US non-provisional application 60/267,183, filed 2/8/2001.

[11] The status of nonprovisional parent application(s) 09/722,441 should also be included. As the parent application has become a patent, the expression "now Patent No. 6,927,046" should follow the filing date of the parent application.

Information Disclosure Statement

[12] All references cited in the IDS filed 9/29/2004 have been considered by the examiner. A copy of Form PTO-1449 is attached to the instant Office action.

[13] If the examiner has inadvertently overlooked an IDS that has previously been filed in the instant application, applicants' cooperation is requested in alerting the examiner to this IDS in the response to this Office action.

Specification/Informalities

[14] The specification is objected to as the table added to the specification in the amendment filed 6/14/2005 improperly identifies the last three constructs. According to the specification, "FCS" in the construct name should be "FC5." Appropriate correction is required.

Claim Objection(s)

[15] Claim 25 is objected to as being grammatically incorrect in the recitation of "encoding any of...or...polypeptides." It is suggested that, for example, applicants amend the phrase to read: "encoding any of...and...polypeptides."

Claim Rejections - 35 USC § 112, Second Paragraph

[16] Claims 2-4, 37, and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 2 is unclear in the recitation of "a nucleic acid encoding a complete...diaminopimelate dehydrogenase...polypeptide" as it is unclear as to the diaminopimelate dehydrogenase polypeptide that applicants consider to be a "complete" polypeptide. It is suggested that applicants clarify the meaning of the claim. In the interest of advancing prosecution, the examiner has interpreted the claim as meaning SEQ ID NO:8 is the intended "complete" polypeptide.

[b] Claim 3 is confusing in the recitation of "wherein said complete ORF2 polypeptide of SEQ ID NO:9 is encoded by a nucleotide sequence at least 90% identical to SEQ ID NO:9." It is unclear as to whether the nucleic acid encodes SEQ ID NO:9 or whether the nucleic acid encodes a polypeptide that is 90% identical to SEQ ID NO:9. It is suggested that applicants clarify the meaning of the claim. In the interest of advancing prosecution, the claim has been interpreted as meaning the nucleic acid encoding a complete ORF2 polypeptide has a nucleotide sequence encoding a polypeptide that is at least 90% identical to SEQ ID NO:9.

[c] Claim 4 is confusing in the recitation of "a nucleic acid encoding...(b) a diaminopimelate dehydrogenase (ddh) polypeptide of SEQ ID NO:8 wherein said ddh polypeptide is complete or truncated" and "a nucleic acid encoding...(c) an ORF2 polypeptide of SEQ ID NO:10, wherein said ORF2 polypeptide is complete or truncated"

as it is unclear as to how a nucleic acid that encodes either SEQ ID NO:8 or SEQ ID NO:10 can simultaneously encode a truncation thereof. It is suggested that applicants clarify the meaning of the claim.

[d] Claim 4 is confusing as the claim recites "further comprises a nucleic acid encoding...a diaminopimelate dehydrogenase (ddh) polypeptide." Claim 4 is dependent upon claim 1, which is drawn to a nucleic acid that comprises a sequence encoding a ddh polypeptide. Thus, according to the limitation of part (b) of claim 4, the nucleic acid of claim 4 would comprise two nucleic acids encoding a ddh polypeptide, which, in view of the disclosure of the specification does not appear to be applicants' intended meaning. It is suggested that applicants clarify the meaning of the claim.

[e] Claim 37 recites the limitation "[t]he vector." There is insufficient antecedent basis for this limitation in the claim.

[f] Claim 39 is unclear in the recitation of "pDElia2$_{FC5}$-KDB2HL" as it is unclear as to the vector construct that is referred to by this term. While the examiner can find a description in the specification of the other vector constructs recited in claim 39, along with a corresponding deposit number (see amendment to specification filed 6/14/2005), the examiner can find no description of a "pDElia2$_{FC5}$-KDB2HL" vector construct. It is suggested that applicants clarify the meaning of a "pDElia2$_{FC5}$-KDB2HL" vector construct.

Claim Rejections - 35 USC § 112, First Paragraph

[17] The new matter rejection of claim 25 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record (¶ 29 of the Office action mailed 3/14/2005) and the reasons stated below.

RESPONSE TO ARGUMENT: Applicants argue the specification supports the limitations of claim 25, pointing to ¶ [0051] and of the specification and Figure 1 of the drawing figures as providing support for the limitations of claim 25.

Applicants' argument is not found persuasive. Support for claim 25 is not provided by the specification for at least two reasons. First, it is noted that claim 25 does not exclude all "lysine pathway polypeptides" other than those recited in claim 1. LysA is disclosed in the specification as being a "lysine pathway polypeptide." However, lysA is absent from claim 25. Second, it is noted that the specification defines "lysine biosynthetic pathway gene" (¶ [0030]) as including "those genes and genes fragments encoding peptides, polypeptides, proteins, and enzymes, which are directly involved in the synthesis of lysine." Figure 1 shows that L-aspartate is a pre-cursor of lysine. As such, according to the definition of "lysine biosynthetic pathway gene," it would appear that the nucleic acid(s) encoding polypeptide(s) involved in the biosynthesis of aspartate, *e.g.,* aminotransferase, which converts oxaloacetate to aspartate (see p. 1747 of Cremer et al., *Appl Environ Microbiol* 57:1746-1752, cited in the IDS filed 9/20/2002), are also encompassed by the definition of "lysine biosynthetic pathway gene." There is no indication of the exclusion of, *e.g.,* aminotransferase, in ¶ [0051] and of the specification and Figure 1 of the drawing figures.

[18] Claims 2-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention. This is a new matter rejection.

MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description".

Claims 2 and 4 recite a nucleic acid encoding a truncated ddh polypeptide that has at least 80% identity to SEQ ID NO:8. Claim 4 recites a nucleic acid encoding a truncated ORF2 polypeptide whose length is at least 25% of the full length of the ORF2 polypeptide of SEQ ID NO:10 and is encoded by a polynucleotide having at least 90% sequence identity to SEQ ID NO:9.

Applicants point to ¶ [0074] of the specification as providing support for the recited limitation of a nucleic acid encoding a truncated ddh polypeptide that has at least 80% identity to SEQ ID NO:8. The examiner can find no support for this limitation at ¶ [0074] or any other disclosure of the specification, claims, and/or drawings as originally filed for the recited limitation.

In the response filed 6/9/2004, applicants point to ¶ [0060] and [0066] of the specification as providing support for the recited limitation of a nucleic acid encoding a

truncated ORF2 polypeptide whose length is at least 25% of the full length of the ORF2 polypeptide of SEQ ID NO:10 and is encoded by a polynucleotide having at least 90% sequence identity to SEQ ID NO:9. In the response filed 12/7/2004, applicants point to ¶ [0068] of the specification as providing support for the recited limitation. While the examiner can find support for "[a] truncated ORF2 polypeptide has at least about 25% of the full length of an ORF2 polypeptide, preferably the ORF2 polypeptide of SEQ ID NO:10" (¶ [0066]). The examiner can also find support for "a nucleic acid encoding a truncated ORF2 polypeptide would be at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO:13" (¶ [0060]). However, the examiner can find no support for a truncated ORF2 polypeptide encoded by a polynucleotide having at least 90% sequence identity to SEQ ID NO:9, nor can the examiner find support for the combination of a nucleic acid encoding a truncated ORF2 polypeptide whose length is at least 25% of the full length of the ORF2 polypeptide of SEQ ID NO:10 and is encoded by a polynucleotide having at least 90% sequence identity to SEQ ID NO:9.

Applicants are invited to show support for the recited limitations.

[19] Claims 3-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention. This is a new matter rejection.

Claims 3 and 4(c) recite the limitation of a nucleic acid encoding a complete or truncated ORF2 polypeptide, wherein the ORF2 polypeptide increases lysine synthesis. Applicants fail to show support in the specification for variants or truncations of ORF2 having the ability to increase lysine synthesis. While the inherent activity of the ORF2 polypeptide of SEQ ID NO:10, when expressed in an appropriate host cell, may be to increase lysine biosynthesis, this is not necessarily an inherent activity of variants and truncations of ORF2 and applicants should show support for this limitation in the specification, claims, and/or drawings as originally filed. Applicants are invited to show support for the recited limitations.

[20] Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention. This is a new matter rejection.

Claim 4 is drawn to a polynucleotide comprising nucleic acids encoding ask, asd, dapB, and ddh and further comprising a nucleic acid encoding lysA, optionally further comprising a nucleic acid encoding ddh, and optionally further comprising a nucleic acid encoding an ORF2 polypeptide. In the response filed 6/14/2005, applicants failed to show support for the nucleic acid of claim 4. While the examiner can find support for a nucleic acid having the combinations of nucleic acids as set forth in ¶ [0001] of the specification, the examiner can find no support for the combination of nucleic acids as set forth in claim 4. Applicants are invited to show support for the claimed nucleic acid.

[21] Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention. This is a new matter rejection.

Claim 8 recites an ask/asd operon that encodes an ask polypeptide having at least 80% identity to SEQ ID NO:2 and wherein the nucleic acid encoding the ask polypeptide is at least 90% identical to SEQ ID NO:1 and also encodes an ask polypeptide having at least 80% identity to SEQ ID NO:4 and wherein the nucleic acid encoding the ask polypeptide is at least 90% identical to SEQ ID NO:3.

In previous responses, applicants fail to show support for the recited limitation and the examiner can find no support for this limitation. In the absence of support for this limitation in the original application, this is considered to be new matter. Applicants are invited to show support for the recited limitations.

[22] Claims 1-13, 15-23, 25-33, and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of he claimed invention.

Claim 1 (claim(s) 16-23, 25, 30-33, and 37-38 dependent therefrom) is drawn to a genus of nucleic acids encoding an aspartokinase (ask) polypeptide, an aspartate-semialdehyde (asd) polypeptide, a dihydrodipicolinate reductase (dapB) polypeptide,

and a diaminopimelate dehydrogenase (ddh) polypeptide. Claim 2 limits the ddh polypeptide encoded by the nucleic acid of claim 1 to a "complete" ddh polypeptide. Claim 3 is drawn to the nucleic acid of claim 1 additionally comprising a genus of nucleic acids encoding a complete ORF2 polypeptide having a nucleotide sequence encoding a polypeptide that is at least 90% identical to SEQ ID NO:9 and having any function that increases lysine synthesis. Regarding claim 4, in view of the open-ended "encoding" language, the term "nucleic acid encoding...a...truncated...polypeptide of SEQ ID NO:12 having diaminopimelate decarboxylase activity" in claim 4 part (a) (claim(s) 5-6 dependent therefrom) has been broadly interpreted as a nucleic acid encoding any polypeptide that has diaminopimelate decarboxylase (lysA) activity. Claim 4 is drawn to (in relevant part) the nucleic acid of claim 1 further comprising a genus of nucleic acids encoding any polypeptide having lysA activity and encoding a truncated ORF2 polypeptide that has any activity that increases lysine synthesis. Claims 7, 9-11, and 26-29 limit the nucleic acids encoding ask, asd, dapB, ddh, ORF2, and lysA polypeptides to genes from a *Corynebacterium* or a *Corynebacterium glutamicum* cell. Claim 8 limits the nucleic acid encoding the ask and asd polypeptides to an operon encoding an ask polypeptide that has at least 80% identity to SEQ ID NO:2 having any function and has 90% identity to SEQ ID NO:3 and encoding an asd polypeptide that has at least 80% identity to SEQ ID NO:2 having any function and has 90% identity to SEQ ID NO:3. Claim 12 limits the nucleic acid encoding the dapB polypeptide of claim 1 to a nucleic acid having at least 90% identity to SEQ ID NO:5. Claim 13 limits the nucleic acid encoding the ddh polypeptide of claim 2 to a nucleic acid having at least 90% identity to

SEQ ID NO:7. Claim 15 limits the nucleic acid encoding the lysA polypeptide of claim 4 to a nucleic acid having at least 90% identity to SEQ ID NO:11.

The Court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The specification discloses only a single representative species of nucleic acids encoding an ask polypeptide, *i.e.,* SEQ ID NO:1; the specification discloses only a single representative species of nucleic acids encoding an asd polypeptide, *i.e.,* SEQ ID NO:3; the specification discloses only a single representative species of nucleic acids encoding a dapB polypeptide, *i.e.,* SEQ ID NO:5; the specification discloses only a single representative species of nucleic acids

encoding a ddh polypeptide, *i.e.,* SEQ ID NO:7; the specification discloses only a single representative species of nucleic acids encoding a ORF2 polypeptide, *i.e.,* SEQ ID NO:9; and the specification discloses only a single representative species of nucleic acids encoding a lysA polypeptide, *i.e.,* SEQ ID NO:11. Other than these single representative species, the specification fails to disclose any other additional representative species of the genus of claimed polypeptides. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the claimed genus of nucleic acids encompasses species that are widely variant with respect to their structures, including any nucleic acid encoding the respective polypeptide, or functions, including nucleic acids that encode polypeptides having any activity. As such, the disclosure of the single representative species is insufficient to be representative of the attributes and features of all species encompassed by the claimed genus of nucleic acids.

Also, regarding claims 1, 2, 7, 9-11, the CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "[i]n claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly

possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus" and "[a] definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is." Similarly with the claimed genus of nucleic acids, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the nucleic acid species within the genus from other nucleic acids such that one can visualize or recognize the identity of the members of the genus.

Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

RESPONSE TO ARGUMENT: To the extent applicants' arguments are relevant to the instant rejection, applicants' arguments are addressed below.

Applicants argue the specification discloses a representative number of species and the claims recite a common structural feature for all members of the genus of recited nucleic acids encoding ddh and ORF2 polypeptides.

Applicants' argument is not found persuasive. At least for the reasons stated above, the specification fails to describe all members of the genus of recited nucleic acids.

[23] Claims 1-13, 15-33, and 37-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide comprising a nucleic acid encoding the ask polypeptide of SEQ ID NO:2, a nucleic acid encoding the asd polypeptide of SEQ ID NO:4; a nucleic acid encoding the dapB polypeptide of SEQ ID NO:6, and a nucleic acid encoding the ddh polypeptide of SEQ ID NO:8 and optionally further comprising a nucleic acid encoding the ORF2 polypeptide of SEQ ID NO:10 and/or a nucleic acid encoding the lysA polypeptide of SEQ ID NO:12, does not reasonably provide enablement for all polynucleotides broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation is required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each

factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: The claims are so broad as to encompass a nucleic acid encoding any ask polypeptide, any asd polypeptide, any dapB polypeptide, and any ddh polypeptide, optionally wherein the nucleic acid further encodes an ORF2 polypeptide and/or an lysA polypeptide, and optionally wherein the nucleic acid is limited to variants of SEQ ID NO:1, 3, 5, 7, 9, and 11. The enablement provided by the specification is not commensurate in scope with the claim with regard to broad scope of nucleic acids broadly encompassed by the claims. In this case, the specification is enabling only for a nucleic acid encoding SEQ ID NO:2, 4, 6, and 8 and optionally further encoding SEQ ID NO:10 and/or 12.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The amino acid sequence of a polypeptide determines said polypeptide's structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins'

structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions. At the time of the invention, methods for isolating or generating variants of a given polypeptide-encoding nucleic acid were known in the art. However, neither the specification nor the state of the art at the time of the invention provide the necessary guidance for altering the nucleic acids of SEQ ID NO: 1, 3, 5, 7, 9, and 11 with an expectation of obtaining an encoded polypeptide having the desired activity/utility. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). The teachings of Branden et al. are exemplified by the reference of Witkowski et al. (*Biochemistry* 38:11643-11650), which teaches that only a single amino acid substitution results in

conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see *e.g.*, Table 1, page 11647).

The amount of direction provided by the inventor and The existence of working examples: The specification discloses only a single working example of the claimed polypeptide, *i.e.,* a nucleic acid encoding SEQ ID NO:2, 4, 6, and 8 and optionally further encoding SEQ ID NO:10 and/or 12. The specification fails to disclose any *specific* guidance for altering the nucleic acid sequences of SEQ ID NO:1, 3, 5, 7, 9, 11, and 13 with an expectation that the resulting encoded polypeptides as encompassed by the claims will maintain the desired activity/utility.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating or generating variants of an encoded polypeptide were known in the art at the time of the invention, it was not routine in the art to screen – by a trial and error process – for all nucleic acids encoding variants of SEQ ID NO:2, 4, 6, 8, 10, and 12 having a substantial number of modifications as encompassed by the claims for those encoded polypeptides having the desired activity/utility.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use

the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Double Patenting Rejection(s)

[24] The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

[25] Claims 1-13, 15-23, and 25-39 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-24 and 27-31 of pending application 10/771,695. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined claim is not patentably distinct from the reference claim(s) because the claim

is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each. Claims 17, 31, and 34 are generic to all that is recited in claim 31 of the '695 application. That is, claim 31 of the '695 application anticipates claims 17, 31, and 34. Also, claims 1-13, 15-16, 18-30, 32-33, and 35-39 cannot be considered patentably distinct over claims 19-24 and 27-30 of the '695 application when there are specifically disclosed embodiments in the '695 application that support claims 19-24 and 27-30 and falls within the scope of claims 1-13, 15-16, 18-30, 32-33, and 35-39 herein because it would have been obvious to one of ordinary skill in the art to make the nucleic acid, vector, host cell, and methods of claims 1-13, 15-16, 18-30, 32-33, and 35-39 herein because they are specifically disclosed embodiments that support claims 19-24 and 27-30 in the '695 application. One of ordinary skill in the art would have been motivated to make the nucleic acid, vector, host cell, and methods as recited in claims 1-13, 15-16, 18-30, 32-33, and 35-39 herein because these embodiments are disclosed as being preferred embodiments within claims 19-24 and 27-30 of the '695 application.

Citation of Relevant Prior Art

[26] The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The examiner considers Kojima et al. (US Patent 6,040,160; cited in the IDS filed 9/20/2002) to be the reference that is most relevant to the claimed

invention. The reference of Kojima et al. teaches that enhanced expression of nucleic acids encoding aspartokinase (lysC), dihydrodipicolinate reductase (dapB), and diaminopimelate dehydrogenase (ddh) polypeptides result in increased production of L-lysine. While Kojima et al. teach aspartate semialdehydedehydrogenase (asd) is involved in the biosynthesis of lysine (column 30), the reference provides no motivation to enhance expression of asd. Kojima et al. teaches that asd is not a rate limiting enzyme in the production of L-lysine and overexpression of dapA, lysC, dapB, and ddh, all of which were determined to be rate-limiting, and further teaches that co-expression of dapA, lysC, dapB, ddh, and asd actually reduced the amount of L-lysine in the culture medium (column 35, Table 4).

Conclusion

[27] Status of the claims:

Claims 1-13 and 15-42 are pending.

Claims 24 and 40-42 are withdrawn from consideration.

Claims 1-13, 15-23, and 25-39 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Friday, 7:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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